REMARKS

Amendments

Claim 19 has been amended to limit the claims to methods of promoting bone marrow cell proliferation by the administration of unglycosylated recombinant human alpha-fetoprotein. Support for this amendment is found in now-cancelled dependent claim 20. Claim 21 has been amended to revise dependency in view of the cancellation of claim 20. No new matter has been added by these amendments.

Rejection Under § 112, first paragraph

Applicant's specification stands objected to, and claims 19-22 stand rejected under 35 U.S.C. § 112, ¶ 1 on the ground that the specification fails to teach how to make and/or use the claimed invention, i.e., fails to provide an enabling disclosure. For the reasons given below and in view of the above claim amendments, this rejection is respectfully traversed.

The first basis of the rejection is the assertion that the specification does not enable the claimed invention because applicant's *in vitro* results fail to demonstrate the effectiveness of recombinant human alpha-fetoprotein (rHuAFP) for promoting growth of bone marrow cells *in vivo*. In particular, the examiner postulates that it is not known whether rHuAFP will retain its biological activity when administered through standard pharmacological routes because immunological reactions may neutralize the desired biological properties of rHuAFP *in vivo*. This belief is unwarranted.

First, as is recognized by the examiner, applicant's *in vitro* results are in fact predictive of *in vivo* success:

> "[O]ne would expect that the results obtained with murine bone marrow in vitro would be predictive of success in vivo. "[Office Action mailed April 4, 1994, page 9.]

There is no reason to believe that once applicant showed that unglycosylated rHuAFP stimulated the proliferation of bone marrow cells *in vitro* that similar results would not have been achieved *in vivo*.

In addition, applicant points out that this basis for the § 112 rejection -- while cast in enablement terms -- is, in reality, a utility rejection and should be properly evaluated under the Utility Examination Guidelines published in the Federal Register in July 1995 and now cited in the MPEP at 703.06(a)(1) and 2107-2107.02. These Guidelines and the accompanying Legal Analysis apply to rejections based upon lack of utility, whether cited under 35 U.S.C § 101 or under § 112, first paragraph, as in the present case. The standard is whether the efficacy of a therapeutic is believable to those skilled in the art. Moreover, as noted in the Guidelines, to uphold this ground for the § 112 rejection, the examiner must establish the present case as one of those rare instances which meets the stringent criteria for rejection described in the Legal Analysis, i.e., "totally incapable of achieving a useful result." Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555 (Fed. Cir. 1992), as cited in the Legal Analysis, page 2, lines 44-45. According to the Legal Analysis, the only instances in which the Federal

courts have found a lack of patentable utility was where, "based upon the factual record of the case, it was clear that the invention could and did not work as the inventor claimed it did." (Legal Analysis page 3, lines 10-12). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention or (b) asserted a utility that could be true only "if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." (Legal Analysis page 9, lines 10-16).

Clearly, no such evidence is present in this case. The claimed the method of promoting bone marrow cell proliferation violates no scientific principle or law of nature, and, in fact, this method has been shown to be efficacious using a reliable *in vitro* assay. Furthermore, applicant's approach for using rHuAFP is consistent with contemporary knowledge in the field of medicine and immunology, and no evidence to counter this assertion has been made of record in this case.

Furthermore, those skilled in the art would have no doubt that the utility claimed for this invention is indeed **credible.** As the Guidelines say,

> "The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use."

In view of the above evidence, it is clear that there is a "reasonable correlation between the activity and the asserted use" thus, applicant has clearly met the standard set forth in the Guidelines. For all of the above reasons, applicant requests reconsideration and withdrawal of this first basis for the enablement rejection.

Second, applicant points out that the examiner's conclusion that adverse immunological reactions would neutralize the biological activity of rHuAFP *in vivo* is incorrect. Examples in the literature discuss circumstances where antibodies are raised against recombinant human proteins without affecting the desired biological activity. For example, as noted in the *Physicians' Desk Reference*, despite developing antibodies to recombinant human growth hormone (rHGH), patients receiving rHGH ("Humatrope") still experienced increases in linear growth and other salutary effects of recombinant HGH. Furthermore, the patients did not experience any unusual side effects (see Appendix I).

As a second ground for rejection, the examiner asserts that the specification fails to instruct the skilled artisan on a therapeutic regimen, e.g., route of, duration of, and quantity of administration, for promoting bone marrow cell proliferation using rHuAFP. In particular, the examiner contends that since applicant has not specifically taught such regimens for human therapy, it would require undue experimentation to practice the claimed invention. The examiner relies on In re Colianni (195

U.S.P.Q. 150, CAFC) in making this rejection. This rejection should be withdrawn.

In the first place, applicant, at pages 19-22 of the specification, has provided clear guidance on therapeutic regimens useful for administering rHuAFP, including routes of administration, dosage, and duration of administration. In addition, recombinant human proteins such as insulin and HGH are routinely used as therapeutics for treating human disorders. These proteins are produced in microorganisms, purified, and injected into patients to achieve the desired effect. For persons who have diabetes, recombinant insulin is administered by daily injections. In addition, persons requiring growth hormone therapy are given rHGH (e.g., Humatrope) injections, either daily or several times per week. Similarly, as described in applicant's specification at pages 20-21, rHuAFP may be administered by injection. Accordingly, there can be no doubt that determination of the parameters for administration of rHuAFP, like determination administration routine for recombinant insulin and HGH, is also well within the skill of those in the art.

The appropriate dosage designating the route, duration and quantity of administration, for any human biologic drug, including rHuAFP, is readily determined through routine Food and Drug Administration (FDA)-approved clinical trials without undue experimentation. In fact, appropriate parameters for treatment of humans can only be determined in clinical trials. Drugs used to treat people must be tested in people. Such clinical trials

determine if a drug is safe and effective, at what doses it works best, and what side effects it causes. Controlled clinical trials, in which results observed in patients administered the drug are compared to the results in similar patients receiving a different treatment, are therefore used to determine drug dosage and efficacy. These controlled clinical trials are the only legal basis for the FDA to conclude the appropriate dosage that a new drug has been shown to be effective. Such clinical trials are conducted using conventional methods, and do not constitute undue experimentation.

Moreover, the examiner's reliance on In re Colianni is misplaced. The specification at issue in Colianni did not include even one "single specific example of embodiment by way of illustration of how the claimed method is practiced." 195 U.S.P.Q 152. In contrast to Colianni, applicant's specification on pages 19-22 provides specific examples for promoting bone marrow cell proliferation. Moreover, applicant's specification provides guidance on dosages useful for promoting bone marrow cell proliferation. Thus, unlike Colianni, applicant has not only provided a working example, but has also taught persons skilled in the art how to obtain appropriate dosages for practicing the claimed invention.

As a third basis for rejection, the examiner points out that a 1978 abstract co-authored by the applicant shows that HuAFP has suppressive effects on human bone marrow derived cells and that this observation "runs counter to the intended use language of the claims which recite a method of promoting bone

marrow proliferation." The examiner has misinterpreted the abstract involving the suppression of reactions by fully-differentiated mature T-cells isolated from human peripheral blood using HuAFP. The abstract addresses responses of T-cell and B-cells isolated from human peripheral blood, not proliferation of immature bone marrow cells. Not only is this an "apples and oranges" comparison, but, in this specific case, established biological differences between the different cell types render the comparison inappropriate. Because of these differences, there is no reasonable basis for concluding that therapeutics for promoting the growth of bone marrow cells involving the use of rHuAFP generally are unpredictable.

In view of the above remarks, applicant respectfully requests the examiner to reconsider and withdraw the objection to the specification under 35 U.S.C. § 112, ¶ 1, and find that applicant's specification enables the claimed invention.

Rejections Under 35 U.S.C. § 103

Claims 19-21 stand rejected under 35 U.S.C. § 103 as unpatentable over Hoskin et al. ("CB", "CC", and "CD"). The examiner states that "one would expect that results obtained with murine bone marrow cells *in vitro* would be predictive of success *in vivo*, absent results to the contrary." In addition, the examiner concludes that there is no patentable distinction between rHuAFP, purified non-recombinant HuAFP, and glycosylated rHuAFP, and unglycosylated HuAFP.

The Hoskin references, either alone or in combination,

do not render the presently claimed invention obvious.

Crucial to applicant's claimed invention is the finding that rHuAFP remains biologically active when in the unglycosylated state, i.e., when made in recombinant prokaryotic cells. This is a significant advance. It could not have been predicted *a priori* that the unglycosylated form of HuAFP would be biologically active. Accordingly, applicant's results are central to the invention; especially because none of the Hoskin references provides, motivates, or suggests the invention. The Hoskin references never even discuss rHuAFP, much less indicate that the normally heavily glycosylated HuAFP might be biologically active in an unglycosylated state. The Hoskin references thus cannot render the claimed invention obvious.

Based the above amendments and remarks, applicant requests reconsideration and withdrawal of the § 103 rejection.

Conclusion

Applicant submits that all of the claims are now in condition for allowance, which action is respectfully requested. If the Examiner does not agree with this conclusion, he is requested to call the undersigned to arrange a telephone interview.

On August 20, 1996, Applicant filed a petition to extend the response deadline through October 4, 1996. Accordingly, no fee is believed due at this time. Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: October 4, 1996

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